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Prognostic Factors after Extended Esophagectomy for Squamous Cell Carcinoma of the Thoracic Esophagus

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Backgrounds and Objectives: In Japan, extended esophagectomy with extensive lymphadenectomy has become the standard surgical procedure for carcinoma of the thoracic esophagus. Although mortality and morbidity rates after such extensive esophagectomy have been acceptable, the long-term outcomes are not necessarily satisfactory.

Methods: Among 235 patients with primary squamous cell carcinoma of the thoracic esophagus between June 1981 and March 1998, 143 patients (60.9%) underwent extended esophagectomy with extensive lymphadenectomy. To exclude the effects of surgery-related postoperative complications, 14 patients who died within 90 days after operation were excluded. Thus, clinicopathological characteristics and prognostic factors of 129 patients were retrospectively investigated.

Results: Sixty-three patients were alive and free of cancer. Sixty-six patients died: 37 of recurrence of the esophageal cancer and 29 of other causes. The 1-, 3-, 5-, and 10-year overall survival rates in the 129 patients were 78.8%, 53.5%, 45.8%, and 30.9%, respectively, and the disease-specific survival rates were 85.7%, 69.1%, 67.9%, and 56.2%, respectively. The factors influencing the disease-specific survival rate were tumor location (upper third vs. non–upper third), Borrmann classification (0, 1 vs. 2, 3), size of tumor ($\leq$3.0 vs. >3.0 cm), depth of invasion (T1, 2 vs. T3, 4), number of lymph node metastases (0 or 1 vs. $\geq$2), time of operation ($\leq$420 vs. >420 min), amount of blood transfused ($\leq$2 vs. $\geq$3 U), lymph vessel invasion (marked vs. not marked), and blood vessel invasion (marked vs. not marked). Among those significant variables, independent prognostic factors for survival determined by multivariate analysis were number of lymph node metastases ($P < 0.001$), amount of blood transfusions ($P = 0.0016$), and tumor location ($P = 0.0382$).

Conclusions: Patients with a single metastatic node after extended esophagectomy should be considered to have excellent prognosis, like patients with pN0 tumors. Patients with multiple involved nodes should receive aggressive postoperative adjuvant treatments. Reduced blood loss during

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extended esophagectomy and minimal blood transfusions might improve the outcome of curative esophageal resections.

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KEY WORDS: esophageal cancer; extended esophagectomy; three-field lymphadenectomy; prognostic factor; long-term result

INTRODUCTION

The operative approach for esophageal cancer varies from standard transthoracic esophagectomy chiefly for palliation [1], to *en bloc* esophagectomy for a curative operation [2], to limited excision without thoracotomy [3]. Since the early 1980s, esophagectomy along with three-field extensive lymph node dissection has become the standard surgical procedure to achieve an accurate pathological staging and better prognosis in Japan [4–6], and thus also encouraged the early introduction of such extended esophagectomy in Western countries [7,8]. Although mortality and morbidity rates after such esophagectomy have been acceptable, the long-term outcomes are not necessarily satisfactory [4–6,9,10]. Until now, detailed analyses of prognostic factors after such esophagectomies have not been available, and it is important to evaluate which patients benefit from such an aggressive surgery.

We have been performing extended esophagectomies for patients with potentially curable squamous cell carcinoma of the thoracic esophagus since June 1981. In this study, we retrospectively assessed the clinicopathological features and prognostic factors of 129 patients who had undergone extended esophagectomy with 3-field lymphadenectomy in our institution.

MATERIALS AND METHODS

Between June 1981 and March 1998, 235 patients with primary squamous cell carcinoma of the thoracic esophagus were admitted to the Second Department of Surgery, Shimane Medical University. Among those, 190 patients (80.9%) underwent esophagectomy, 4 patients (1.7%) received endoscopic mucosal resection, and the remaining 41 patients (17.4%) had palliative treatments: bypass in 7, stomy in 6, radiochemotherapy in 25, chemotherapy in 1, and no treatment in 2. Of 190 surgically treated patients, 143 (75.3%) underwent curative esophagectomy (R0) [11]. To exclude the effects of surgery-related postoperative complications on long-term survival, 14 patients (9.8%) who died within 90 days after the operation were excluded. Therefore, 129 patients were enrolled in this analysis.

The majority of these patients underwent a right transthoracic subtotal esophagectomy along with 3-field lymph node dissection including the cervical (bilateral supraclavicular regions), mediastinal (around the esophagus and trachea including around the bilateral recurrent laryngeal nerves), and abdominal (perigastric region and around the celiac axis) lymph nodes. Reconstruction was usually carried out with a gastric tube through the retrosternal route, and esophagogastrostomy was done in the neck under cervical incision and laparotomy.

The patients with superficial esophageal cancer did not receive any adjuvant treatment. When the tumor invaded deeper submucosal or shallow muscle layers, 1 or 2 cycles of postoperative chemotherapy were administered. According to a prospective protocol, pre- and postoperative radiochemotherapies were routinely administered in advanced cases. Patients received 2 cycles of the same regimen postoperatively. One cycle of chemotherapy consisted of bolus administration of cisplatin (50 mg/m^2/day) on the 1st and 15th day and fluorouracil (300 mg/m^2) for 28 days by continuous intravenous infusion. One cycle of radiotherapy consisted of 1.8 Gy daily directed to the tumor bed. The total dosage was 30.6 Gy.

Clinicopathological characteristics of 129 patients were retrospectively investigated based on the TNM classification of malignant tumors [11]. The outcome of patients was examined, and those who clearly died of recurrences were regarded as tumor-related deaths. In calculating the 10-year disease-specific survival rate, 6 patients who were alive and 1 patient who died of a cause other than esophageal cancer after >10 years were counted as being alive at 10 years. The patients who died of causes other than esophageal cancer were classified as being alive at the end point.

The survival rates were estimated by the Kaplan-Meier method [12], and the statistical analysis was carried out by the log-rank test to test for equality of the survival curves. In multivariate analysis, independent prognostic factors were determined using a Cox proportional hazards model [13] (StatView J4.5: Abacus Concepts, Inc., Berkeley, CA). The level of significance was $P < 0.05$.

RESULTS

Outcomes

At the time of this analysis, 63 patients were alive and free of cancer, and 66 patients were dead. Of those 66 deaths, the causes were recurrence of the esophageal cancer in 37 and other in 29: pneumonia in 8, senility in 6, other malignancies in 5, heart-related problems in 3, gastric tube ulcer perforation in 2, unknown in 2, and cerebrovascular attack, liver failure, and cholecystitis in 1

TABLE I. Clinicopathological Features and Disease-Specific Survival Rates of Patients with Resectable Esophageal Cancer

Variable	No. (%)	Survival rate (%)				P^a
		1 year	3 years	5 years	10 years	
Gender						
Female	10 (7.8)	77.8	51.9	51.9	51.9	NS
Male	119 (92.2)	85.5	67.5	65.8	56.7	
Age (years)						
<65	70 (54.3)	85	67.2	61.7	61.7	NS
≥65	59 (45.7)	84.9	69.7	69.7	52	
Tumor location						
Upper	16 (12.4)	64.6	35.9	35.9	35.9	0.0059
Middle, lower	113 (87.6)	87.8	73.2	69.7	60	
Borrmann classification						
0, 1	53 (41.1)	97.6	89.6	89.6	82.7	<0.0001
2, 3	76 (58.9)	76.3	54.2	46	40.9	
Tumor size, cm						
≤3.0	38 (29.5)	100	91.6	91.6	81.5	0.0012
>3.0	91 (70.5)	80.3	59.4	55.3	46.1	
No. of lymph nodes dissected						
<35	61 (47.3)	89.6	73.4	73.4	65.7	0.1050
>36	68 (52.7)	83.7	62.7	55.4	47.5	
Depth of invasion						
pTis,1,2	88 (68.2)	93.4	84.2	79.7	76	<0.0001
pT3,4	41 (31.8)	66.8	35.2	35.2	—	
No. of involved lymph nodes						
0 or 1	79 (61.2)	95.7	90.7	90.7	78.7	<0.0001
≥2	50 (38.8)	67.4	31.6	19.7	—	
Time of operation, min						
≤420	92 (71.3)	84.7	74.5	72.3	69.1	0.0378
>420	37 (28.7)	85.2	53.6	48.7	36.1	
Amount of blood transfused, U						
≤2	58 (45)	93.7	83.6	80.1	74.4	0.0027
≥3	71 (55)	78.4	56.9	54.2	45.3	
Histological differentiation						
Well	44 (34.1)	86.5	66.3	62.2	57.4	NS
Not well	85 (65.9)	81.7	72.1	72.1	49.4	
Lymph vessel invasion						
Negative	86 (66.7)	91	80.9	76.9	66.7	<0.0001
Positive	43 (33.3)	70.3	38.4	38.4	—	
Blood vessel invasion						
Negative	110 (85.3)	90.6	73.6	70.2	60.9	0.0002
Positive	19 (14.7)	49.5	35.4	35.4	—	
Radiotherapy						
Yes	75 (58.1)	81	62.2	57.9	50.9	NS
No	54 (41.9)	91	78.6	78.6	65.5	
Stage						
0, I, II	76 (58.9)	100	91.6	91.6	83.8	<0.0001
III, IV	53 (41.1)	67	33.5	25.5	17	

[a]NS = not significant.

each. The longest recurrence-free survival was 6.9 years after esophagectomy.

Adjuvant Treatment

Seventy-five patients received adjuvant radiochemotherapy. Thirty-five patients with superficial esophageal cancer did not receive any adjuvant treatment. Sixteen patients received postoperative chemotherapy. Forty-two patients with advanced tumor had pre- and postoperative radiochemotherapy, and 33 patients received only 2 cycles of postoperative radiochemotherapy. The remaining 3 patients refused any adjuvant treatment.

Clinicopathological Factors Influencing Survival Rate

Table I shows the clinicopathological variables influencing the cumulative survival rates by the univariate analysis. The factors influencing survival rate were tumor location (upper third vs. non–upper third), Borrmann classification (0, 1 vs. 2, 3), tumor size (≤3.0 vs. >3.0

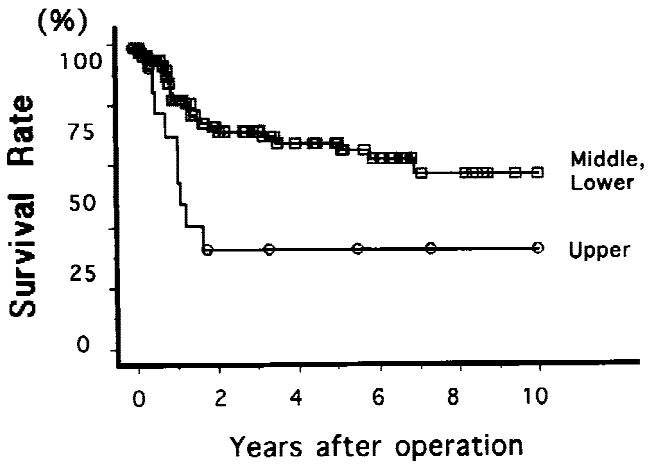

Fig. 1. Cumulative disease-specific survival curves in terms of tumor location. Median survival time for patients with middle thoracic esophageal cancer ($n = 70$) was 23.8 months, those with lower thoracic cancer ($n = 43$) 18.7 months, and those with upper thoracic cancer ($n = 16$) 14.5 months. The 3- and 5-year survival rates were, respectively, 35.9% and 35.9% for those with upper thoracic cancer ($n = 16$) and 73.2% and 69.7% for those with tumors in other locations ($n = 113$) (log-rank, $P = 0.0059$).

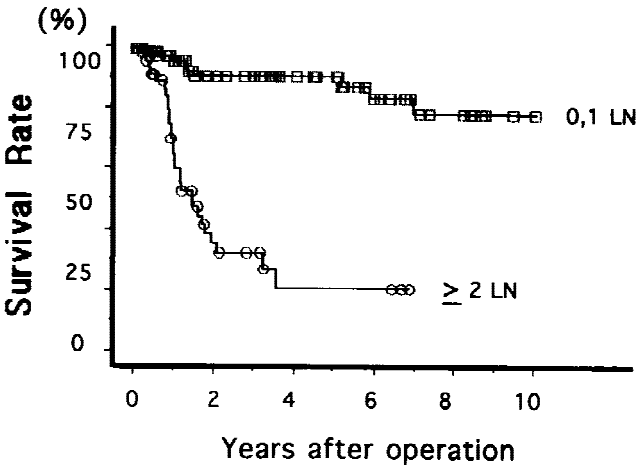

Fig. 2. Cumulative disease-specific survival curves in terms of the number of involved lymph nodes. Median survival time for patients without lymph node metastasis ($n = 62$) was 37.7 months. For those with 1 infiltrated node it was ($n = 17$) 54.8 months, those with 2 diseased nodes ($n = 15$) 15.1 months, those with 3 nodes ($n = 4$) 3.6 months, those with 4 nodes ($n = 4$) 7 months, and those with more than 5 infiltrated nodes ($n = 27$) 11.9 months. The 3- and 5-year survival rates were, respectively, 31.6% and 19.7% for those with ≥2 positive nodes ($n = 50$) and 90.7% and 90.7% for those with <2 nodes ($n = 79$) (log-rank, $P < 0.0001$).

cm), depth of invasion (T1, 2 vs. T3, 4), number of involved lymph nodes (0, 1 vs. >2), operation time (<420 vs. >420 min), amount of perioperative blood transfused (≤2 vs. ≥3 U), lymph vessel invasion (marked vs. not marked), and blood vessel invasion (marked vs. not marked). Gender, histological differentiation, and radiochemotherapy did not influence the survival rate.

The 1-, 3-, 5-, and 10-year overall survival rates of all 129 patients were 78.8%, 53.5%, 45.8%, and 30.9%, respectively, and the disease-specific survival rates were 85.7%, 69.1%, 67.9%, and 56.2%, respectively. The 5- and 10-year disease-specific survival rates for stage 0/I were 100% and 83.3%, for stage IIA 89.2% and 80.2%, for stage IIB 79.4% and 79.4%, for stage III 31.6% and 0%, and for stage IV 17.1% and 17.1%, respectively. Cumulative disease-specific survival curves in terms of tumor location, number of involved lymph nodes, and amount of perioperative blood transfusion are shown in Figures 1, 2, and 3, respectively.

Prognostic Significance Evaluated by the Multivariate Analysis

Among those nine significant variables evaluated by the univariate analysis, independent prognostic factors for survival as determined by the multivariate analysis were number of involved lymph nodes (0 or 1 vs. ≥2, $P < 0.0001$), amount of blood transfusions (≤2 vs. ≥3, $P = 0.0016$), and tumor location (upper third vs. non–upper third, $P = 0.0382$) (Table II).

Additional multivariate analysis was done including the TNM stage of the disease as a covariate. As pT and pN are integral parts of the TNM tumor stage, from this

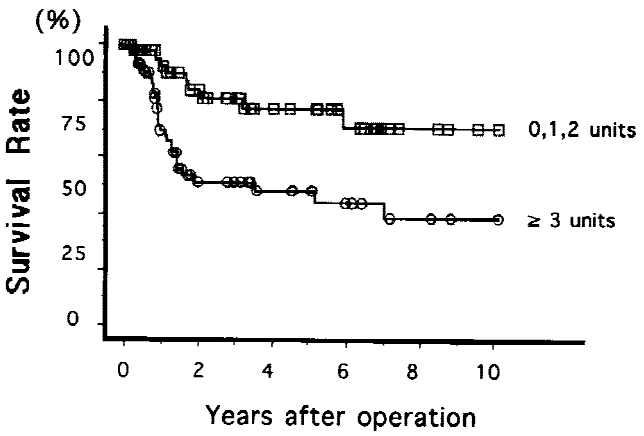

Fig. 3. Cumulative disease-specific survival curves in terms of amount of blood transfused. Median survival time for patients without blood transfusion ($n = 31$) was 15.1 months. For those with 1 or 2 U transfused ($n = 27$) 39 months, those with 3 or 4 U transfused ($n = 33$) 14.8 months, and those with ≥5 U transfused ($n = 38$) 18 months. The 3- and 5-year survival rates were, respectively, 56.9% and 54.2% for those with a high amount (≥3) transfused ($n = 71$) and 83.6% and 80.1% for patients with no or few (≤2) transfusions ($n = 58$) (log-rank, $P = 0.0027$).

analysis we excluded pT factor and number of involved lymph nodes for a more appropriate analysis of the independent prognostic factor. Therefore, in this additional analysis, the stage of disease (0, I, II vs. III, IV, $P < 0.0001$) and amount of blood transfused ($P = 0.0002$) became independent prognosticators of esophageal carcinoma patients. However, tumor location lost its significance as an independent prognosticator ($P = 0.0931$).

A further multivariate analysis, considering overall

TABLE II. Multivariate Analysis of Prognostic Factors for Disease-Specific Survival Using Cox's Proportional Hazard Model

Parameter[a]	Coefficient	*P*	Hazard ratio	95% confidence interval
No. of involved lymph nodes	2.112	<0.0001	8.265	3.018–22.637
Units of blood transfused	1.363	0.0016	3.907	1.677–9.102
Tumor location	0.962	0.0382	2.617	1.054–6.500
Blood vessel invasion	0.726	0.1183	2.067	0.831–5.139
Depth of invasion	0.684	0.1126	1.982	0.851–4.615
Borrmann classification	0.606	0.2785	1.833	0.612–5.488
Size of tumor	0.345	0.6266	1.412	0.352–5.662
Time of operation	0.241	0.5040	1.272	0.628–2.578
Lymph vessel invasion	−0.090	0.8435	0.914	0.375–2.229

[a]Parameters are categorized in Table I.

survival as the end point of the disease, was done to determine the independent prognostic factor (data not shown). The number of involved lymph nodes ($P < 0.0001$) and amount of blood transfused ($P = 0.0002$) became the strongest negative prognostic indicators, followed by blood vessel invasion ($P = 0.0207$). Tumor location did not become an independent prognosticator ($P = 0.1758$), because only 2 patients with the upper-third tumor died of unrelated causes to esophageal cancer, whereas 15 with middle and 12 with lower-third cancer died of miscellaneous causes other than esophageal cancer.

DISCUSSION

The most frequent sites of recurrence after esophagectomy are mediastinal locoregional areas, so 3-field extensive lymph node dissection during esophagectomy was started and has become the standard surgical procedure to obtain accurate pathological staging and improve surgical results in Japan [4–6] and in Western countries [7,8]. Although mortality and morbidity rates after such esophagectomies have been acceptable by recent advances in surgical techniques, certain numbers of patients develop recurrences, and the long-term outcomes of these patients are not necessarily satisfactory [4–6,9,10]. Thus, it is necessary to evaluate which patients are benefited by extended esophagectomy and to know the prognostic factors.

According to published reports [4,14], upper thoracic esophageal carcinoma carries the worst prognosis among all esophageal carcinomas. We showed that 7 of 9 patients with upper thoracic cancer who died had upper mediastinal locoregional recurrences despite extensive lymphadenectomy; patients with upper thoracic esophageal cancers had unfavorable prognoses compared with esophageal cancer in other sites, because of early mediastinal involvement and direct invasion into the tracheobronchial trees. However, 2 challenging experiences, one from the United States [15] and the other from Japan [16], indicated that an extended esophagectomy could be performed, even for upper thoracic esophageal cancer, with low mortality and an acceptable favorable survival rate of 20%–43%. To improve the outcomes of these patients, more meticulous lymphadenectomy around the tracheobronchial trees and bilateral recurrent laryngeal nerves might be important.

The presence or absence of lymph node metastasis is a well known prognostic indicator of esophageal carcinoma. Among the node-positive patients, the number of metastatic nodes clearly influenced survival [5,10,17]. Generally, patients with a large number of diseased nodes had worse survival than those with a few metastatic nodes (e.g., 1–3 vs. ≥4 [17], 1–4 vs. ≥5 [10], 1–7 vs. ≥8 [5]). Our data indicated that patients with a single diseased node had the same long-term survival as pN0 patients, and this factor (≤1 metastatic lymph node) became an independent favorable prognostic factor. Similar data were reported for adenocarcinoma of the esophagus [18]. Thus, patients with a single metastatic node after extended esophagectomy should be considered to have excellent prognosis, like patients with pN0 tumor. However, once the tumor has metastasized to multiple lymph nodes, the disease might be a disseminated one. To improve the survival of patients with multiple lymph node metastases, these patients should receive more aggressive adjuvant treatments than are currently the norm. Before we confirm this, however, the results should be compared with a randomization study.

The perioperative blood transfusions have been associated with tumor recurrence and decreased survival in various types of alimentary tract cancer such as of the colorectum [19], stomach [20], and liver [21]. Despite recent advances in the surgical techniques of esophageal cancer surgery, extensive esophagectomy with meticulous lymphadenectomy produces more blood loss, requiring additional blood transfusions. Our results indicated that large numbers of blood transfusions decreased the survival rate for patients with resectable esophageal cancer. Swisher et al. [22] showed that the shorter survival with high-volume transfusions was a result of an increased number of postoperative complications and that high-volume transfusions were not associated by the

multivariate analysis with increases in tumor recurrence of esophageal cancer. They concluded that blood transfusions did not by themselves decrease the chance of cure after esophageal resection. The reasons for the difference in results between their study and ours remain speculative, but there are several possible explanations. First, Swisher et al. included not only squamous cell carcinoma but adenocarcinomas and others. Second, we excluded the patients who died within 90 days of operation to exclude the effects of surgery-related postoperative complications. Third, Swisher et al. used transfusions of not only blood but also other serum-based products. Fourth, the cut-off point of a "high" amount of blood transfusions was different. Surgeons must be careful to reduce blood loss during extensive esophagectomy and subsequently minimize blood transfusions, not only to avoid risk of infectious diseases but also to reduce tumor recurrence.

Because adjuvant radiochemotherapies administered before and after surgery consisted of various regimens, this did not influence the survival rate and, thus, this might make interpretation of our findings difficult.

In conclusion, patients with a single metastatic node after extended esophagectomy should be considered to have excellent prognosis, like patients with pN0 tumor, and patients with multiple involved nodes should receive aggressive postoperative adjuvant treatments. Reduced blood loss during extended esophagectomy and minimal blood transfusions might improve the outcome of curative esophageal resections.

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